The lectin pathway is initiated by the mannose-binding lectins (MBL) that bind to complex carbohydrate residues on the surface of pathogens. The activation of the classical pathway or the lectin pathway leads to activation of the (C4b2b) C3 convertase.

The alternate pathway is activated by the binding of C3b, which is spontaneously generated by the hydrolysis of C3, on targeted surfaces. This surface-bound C3b is then recognized by factor B, forming the complex C3bB. The C3bB complex, in turn, is cleaved by factor D to yield the active form of the C3 convertase of the AP (C3bBb). Both types of C3 convertases will cleave C3, forming C3b. C3b then either binds to more factor B, enhancing the complement activation through the AP (the so-called alternative or amplification loop), or leads to the formation of the active C5 convertase (C3bBbC3b or C4bC2bC3b), which cleaves C5 and triggers the late events that result in the formation of the membrane attack complex (MAC) (C5b-9).

Inappropriate activation of the complement system is responsible for propagating or initiating pathology in many different diseases, including, for example, C3 glomerulopathy, systemic lupus erythematosus (SLE), *e.g.,* Lupus Nephritis, IgA nephropathy, diabetic nephropathy, polycystic kidney disease, membranous nephropathy, age-related macular degeneration, atypical hemolytic uremic syndrome, thrombotic microangiopathy, myasthenia gravis, ischemia and reperfusion injury, paroxysmal nocturnal hemoglobinuria, and rheumatoid arthritis.

To date, only one therapeutic that targets the alternate pathway, *e.g.,* the C5-C5a axis, is available for the treatment of complement component-associated diseases, the anti-C5 antibody, eculizumab (Soliris®). Although eculizumab has been shown to be effective for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and Myasthenia Gravis, and is currently being evaluated in clinical trials for additional complement component-associated diseases, eculizumab therapy requires weekly high dose infusions followed by biweekly maintenance infusions at a high cost. Furthermore, approximately 50% of eculizumab-treated PNH subjects have low level of hemolysis and require residual transfusions (Hill A, *et al.* (2010) *Haematologica* 95(4):567-73).

Accordingly, there is a need in the art for compositions and methods for treating diseases, disorders, and conditions associated with complement activation by, for example, activation of complement factor B activity.

Summary of the Invention

In one aspect, provided herein is a double stranded ribonucleic acid (dsRNA) agent, or a pharmaceutically acceptable salt thereof, for inhibiting expression of complement factor B (CFB) in a cell,

a) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'-AGUCAUAAAAUUCAGGAAUUCCU-3' of SEQ ID NO: 107,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'-GAAUUCCUGAAUUUUAUGACU-3' of SEQ ID NO: 21,

wherein all of the nucleotides of the sense strand and the antisense strand comprise a nucleotide modification, and

wherein at least one strand is conjugated to a ligand;

b) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'-AUGAAUGAAACGACUUCUCUUGU-3' of SEQ ID NO:521,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'-AAGAGAAGUCGUUUCAUUCAU-3' of SEQ ID NO: 450,

wherein all of the nucleotides of the sense strand and the antisense strand comprise a nucleotide modification, and

wherein at least one strand is conjugated to a ligand;

(c) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'- AGUCATAGCAGUGGAAAGAGAUC-3' of SEQ ID NO: 176,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence 5'- UCUCUUUCCACUGCUAUGACU-3' of SEQ ID NO: 90,

wherein all of the nucleotides of the sense strand and the antisense strand comprise a nucleotide modification, and

wherein at least one strand is conjugated to a ligand;

d) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a nucleotide sequence which differs by no more than 4 nucleotides from the nucleotide sequence 5'- asUfsgaaUfgAfAfacgaCfuUfcucuusgsu-3' of SEQ ID NO: 663,

wherein the sense strand comprises a nucleotide sequence which differs by no more than 4 nucleotides from the nucleotide sequence 5'- asasgagaAfgUfCfGfuuucauucau-3' of SEQ ID NO: 592,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af Cf, Gf, and Uf are 2'- fluoro A, C, G and U, respectively; and s is a phosphorothioate linkage;

e) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a nucleotide sequence which differs by no more than 3 nucleotides from the nucleotide sequence 5'- asUfsgaaUfgAfAfacgaCfuUfcucuusgsu-3' of SEQ ID NO: 663,

wherein the sense strand comprises a nucleotide sequence which differs by no more than 3 nucleotides from the nucleotide sequence 5'- asasgagaAfgUfCfGfuuucauucau-3' of SEQ ID NO: 592,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af Cf, Gf, and Uf are 2'- fluoro A, C, G and U, respectively; and s is a phosphorothioate linkage;

f) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a nucleotide sequence which differs by no more than 2 nucleotides from the nucleotide sequence 5'- asUfsgaaUfgAfAfacgaCfuUfcucuusgsu-3' of SEQ ID NO: 663,

wherein the sense strand comprises a nucleotide sequence which differs by no more than 2 nucleotides from the nucleotide sequence 5'- asasgagaAfgUfCfGfuuucauucau-3' of SEQ ID NO: 592,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af Cf, Gf, and Uf are 2'- fluoro A, C, G and U, respectively; and s is a phosphorothioate linkage;

g) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a nucleotide sequence which differs by no more than one nucleotide from the nucleotide sequence 5'- asUfsgaaUfgAfAfacgaCfuUfcucuusgsu-3' of SEQ ID NO: 663,

wherein the sense strand comprises a nucleotide sequence which differs by no more than one nucleotide from the nucleotide sequence 5'- asasgagaAfgUfCfGfuuucauucau-3' of SEQ ID NO: 592,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af Cf, Gf, and Uf are 2'- fluoro A, C, G and U, respectively; and s is a phosphorothioate linkage;

h) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises the nucleotide sequence 5'-asUfsgaaUfgAfAfacgaCfuUfcucuusgsu-3' of SEQ ID NO: 663,

wherein the sense strand comprises the nucleotide sequence 5'-asasgagaAfgUfCfGfuuucauucau-3' of SEQ ID NO: 592,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af Cf, Gf, and Uf are 2'- fluoro A, C, G and U, respectively; and s is a phosphorothioate linkage;

i) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand consists of the nucleotide sequence 5'-asUfsgaaUfgAfAfacgaCfuUfcucuusgsu-3' of SEQ ID NO: 663,

wherein the sense strand consists of the nucleotide sequence 5'-asasgagaAfgUfCfGfuuucauucau-3' of SEQ ID NO: 592,

wherein a, g, c and u are 2'-O-methyl (2'-OMe) A, G, C, and U, respectively; Af Cf, Gf, and Uf are 2'- fluoro A, C, G and U, respectively; and s is a phosphorothioate linkage;

j)wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7, 13, 16, 19 and 20;

k) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 633-665, 1133-1185, 1133-1173, 1133-1167, 1143-1173, 1540-1563, 1976-2002, 2386-2438, 2386-2418, 2386-2413, and 2389-1418 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8;

l) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 633-655, 643-665, 928-950, 1133-1155, 1140-1162, 1141-1163, 1143-1165, 1145-1167, 1148-1170, 1150-1172, 1151-1173, 1185-1207, 1306-1328, 1534-1556, 1540-1562, 1541-1563, 1976-1998, 1979-2001, 1980-2002, 2078-2100, 2386-2408, 2388-2410, 2389-2411, 2391-2413, 2393-2415, 2395-2417, 2396-2418, 2438-2460, and 2602-2624 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8; or

m) wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 153-175; 202-224; 219-241; 254-276; 304-326; 321-343; 347-369; 402-424; 418-440; 447-469; 491-513; 528-550; 549-571; 566-588; 591-613; 792-814; 819-841; 967-989; 1042-1064; 1234-1256; 1250-1272; 1269-1291; 1335-1357; 1354-1376; 1372-1394; 1422-1444; 1496-1518; 1670-1692; 1716-1738; 1757-1779; 1774-1796; 1793-1815; 1844-1866; 1871-1893; 1909-1931; 1924-1947; 1947-1969; 2161-2183; 2310-2332; 2330-2352; 2355-2377; 2494-2516; and 2527-2549 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO:8.

In another aspect, provided herein is an isolated cell containing the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein.

In another aspect, provided herein is a pharmaceutical composition for inhibiting expression of a gene encoding complement factor B (CFB) comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein.

In another aspect, provided herein is an *in-vitro* method of inhibiting expression of a complement factor B (CFB) gene in a cell, the method comprising contacting the cell with the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, or the pharmaceutical composition as described herein, thereby inhibiting expression of the CFB gene in the cell.

In another aspect, provided herein is use of the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, or the pharmaceutical as described herein, in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in complement factor B expression, or for preventing at least one symptom in a subject having a disorder that would benefit from reduction in complement factor B expression.

In another aspect, provided herein is a kit, a vial, or a syringe comprising the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, or the pharmaceutical composition as described herein.

In yet another aspect, provided herein is the dsRNA agent, or a pharmaceutically acceptable salt thereof, as described herein, or the pharmaceutical composition as described herein for use in therapy.

The present invention provides iRNA compositions which affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding complement factor B (CFB). The complement factor B (CFB) may be within a cell, *e.g.,* a cell within a subject, such as a human subject.

Accordingly, in one aspect the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of complement factor B (CFB) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the